to its toxicity [105]. N-nitroso compounds (NOCs) can induce cancer in multiple organs in at least 40 different animal species, including higher primates [106–108]. In *in vitro* studies on human liver slices, the mechanism of action was shown to be nucleic acid alkylation [109]. Schmahl and Habs commented: "N-nitroso compounds can act carcinogenically in a large number of animal species; there is no rational reason why human beings should be an exception, all the less so since *in vitro* experiments have shown N-nitroso compounds are metabolized in the same way by human livers as by the livers of experimental animals" [108, p. 240]. Several different nitrosylated compounds have been targeted as potential carcinogenic agents, although it is conceded that the long lag time between exposure and tumour development makes it difficult to recognize the links [110]. Dietary N-nitrosyl compounds especially are thought to increase the risk of colon cancer and rectal carcinoma [111, 112].

The Food and Agricultural Organization of the United Nations (FAO) has set a strict upper limit of 1 ppm NNG [113]. The accepted methodology for measuring contamination levels, proposed by Monsanto in 1986 [114], has complicated instrumentation and operation conditions and is relatively insensitive [105]. New advanced methodologies offer safer and more reliable testing methods [115, 105].

One of the pathways by which some bacteria break down glyphosate is by first using carbon-phosphorus lyase (C-P lyase) to produce sarcosine as an immediate breakdown product [89, 116]. Nitrosylated sarcosine is well recognized as a carcinogenic agent. Injection of 225 mg/kg of nitrososarcosine into mice at days 1, 4 and 7 of life led to the development of metastasizing liver carcinomas in later life in 8 out of 14 exposed animals [117].

Elevated levels of sarcosine are also linked to prostate cancer, particularly metastatic prostate cancer [118]. An unbiased metabolomic survey of prostate cancer patients identified elevated levels of serum or urinary sarcosine as a marker of aggressive disease [119] (prostate cancer is the most commonly diagnosed cancer in men in the USA, and it afflicts one in nine men over the age of 65 [120]). In both *in vitro* and *in vivo* prostate cancer models, exposure to sarcosine, but not glycine or alanine, induced invasion and intravasation [119].

10. IMPAIRED GLYCINE SYNTHESIS

Perhaps surprisingly, a recent study has proposed that glyphosate might serve a useful rôle in cancer treatment due to its ability to inhibit glycine synthesis [121]. Glycine is essential for the synthesis of DNA and, therefore, for cell proliferation. *In vitro* studies on 8 different cancer cell lines (including prostate, ovarian, cervical and lung cancer) demonstrated that glyphosate at doses ranging from 15 to 50 mM was cytotoxic to tumour cells, and that cytotoxicity to normal cell lines required higher doses (e.g., 100 mM). It was hypothesized that the mechanism of action involved impaired glycine synthesis due to glyphosate acting as a glycine mimetic.

In direct contradiction, however, glycine has been shown to prevent tumorigenesis [122] and it is a potent anti-angiogenic nutrient that suppresses tumour growth, possibly through activation of a glycine-gated chloride channel [123]. Impaired glycine synthesis likely has other adverse effects as well, such as the possibility that glyphosate interferes with glycine conjugation of benzene-based compounds. In particular, this is a mechanism used by gut microbes, particularly *Bifidobacteria*, to detoxify phenolic compounds, producing hippurate (benzoylglycine), a glycine conjugate of benzoic acid, as a mechanism for detoxification [124]. Glycine has been shown to be a limiting factor for hippurate production [125]. We stated earlier that glyphosate preferentially harms Bifidobacteria [46], and studies have shown reduced counts of Bifidobacteria in obese rats along with reduced excretion of hippurate [126]. Obese humans have also been shown to have reduced urinary hippurate [127]. Furthermore, lower urinary hippurate is linked to ulcerative colitis, particularly Crohn's disease [128]. A Swedish study of over 21 000 Crohn's disease patients identified increased risk of a broad range of cancers, including liver, pancreatic, lung, prostate, testicular, kidney, squamous cell skin cancer, nonthyroid endocrine tumours and leukaemia [129]. Crohn's and inflammatory bowel disease have been increasing in incidence in the USA in step with the increase in glyphosate usage on corn and soy crops ($R = 0.938, P \leq 7.1 \times 10^{-8}$) [1].

11. COLON AND LIVER CANCER

As shown in Table 1, the incidence of liver cancer in the USA has increased substantially in the past two decades, *pari passu* with the increase in glyphosate usage on corn and soy crops ($P \leq 4.6) \times 10^{-8}$.

Nonalcoholic steatohepatitis (NASH) is a fatty liver disease that has been linked to excess dietary fructose [130]. We hypothesize that it is due primarily to the disruption in gut metabolism of fructose due to glyphosate blocking the shikimate pathway, as discussed previously. Fructose, which should have been processed in the gut leading to production of aromatic amino acids, instead is delivered to the liver, which converts it into fat for either local storage or distribution within low-density lipid particles (LDL). NASH affects a large proportion of the US population and is increasing in prevalence worldwide

with adoption of a "Western diet" [131]. NASH causes cirrhosis and increases risk of liver cancer [131, 132]. Hepatocellular carcinoma (HCC) is the most common cause of obesity-related cancer deaths among middle-aged men in America. The consumption of refined carbohydrates in soft drinks has been postulated to be a key factor in the development of NASH [130]. As we have seen, soft drinks containing HFCS are very high in methylglyoxal.

A study from 1988 on children with severe chronic liver disease revealed that those children with low vitamin E levels were susceptible to H_2O_2-induced haemolytic anaemia [133]. We earlier discussed the rôle of glyphosate in depleting vitamin E. Haemolysis leads to haemochromatosis (release of free iron from haem). The endocrine glands, heart, liver, testes and pancreas are all affected by haemochromatosis. Damage to pancreatic islet β-cells from iron deposition can lead to cellular death and functional impairment associated with diabetes [134]. Other effects of haemochromatosis include bone and joint pain, arthritis, cardiomyopathy and testicular problems.

The liver synthesizes substantial amounts of haem, which is needed primarily for the cytochrome P450 (CYP) enzymes, which perform many important rôles, including bile acid synthesis, hormone activation and breakdown, and detoxifying many carcinogenic agents, including phenolic and other organic xenobiotics as well as drugs and bilirubin. Glyphosate likely contributes to the destruction of CYP enzymes both through H_2O_2 attack at their haem centre as well as through direct interference via nitrosylation at the active site by glyphosate [11]. CYP-mediated drug metabolism is impaired in patients with liver disease, particularly CYP1A, CYP2C19, and CYP3A [135], and this makes these individuals even more susceptible to liver damage.

Inflammation and metabolic disorders are intimately linked, and both are characteristic features of diabetes and obesity [136]. Diabetes and obesity are linked to dramatically higher risk of cancer, particularly of the liver and gastrointestinal tract [137]. This is directly linked to bile acid dysregulation and dysbiosis of the gut microbiome. Elevated levels of cytotoxic secondary bile acids and inflammation induced by an immune response to gut pathogens induce heightened oxidative DNA damage, increased cell proliferation and enterohepatic carcinogenesis [137]. Temporal patterns of glyphosate use on corn and soy crops strongly correlate with the increase in both diabetes and liver cancer observed over the same time interval [1].

Gut dysbiosis, due in part to glyphosate's antimicrobial effects, leads to gut inflammation and impairment of the gut barrier function. This means that pathogens will escape the gut and infiltrate the liver. Exposure to endotoxin produced by gut microbes, such as lipopolysaccharides (LPS) leads to inflammation in the liver along with hepatic fibrosis [138]. Several types of chronic liver disease are associated with increased levels of bacterial LPS in the portal and/or systemic circulation [139].

Acute hepatic porphyrias are disorders caused by enzyme defects in haem biosynthesis [140], and they are risk factors for liver cancer [141–143]. Glyphosate has been shown to disrupt haem synthesis, by suppressing the enzyme that activates the first step, combining glycine with succinyl coenzyme A to form δ-aminolevulinic acid [144]. An often-overlooked component of glyphosate's toxicity to plants is inhibition of chlorophyll synthesis [145], as δ-aminolevulinic acid is also a precursor to chlorophyll as well as haem.

γ-glutamyl transferase (GGT) is a membrane-bound enzyme that decomposes glutathione into cysteinyl glycine and glutamate; it is highly expressed in the liver. Excess serum GGT has been linked to both oxidative stress [146] and increased cancer risk [147] as well as many other diseases [148]. In a study on 283 438 people who were divided into five subgroups based on GGT level, a hazard ratio of 18.5 for risk of hepatic carcinoma was ascertained for the highest level compared to the lowest [149]. Another study based in Korea found an increased risk of multiple cancers in association with elevated GGT: most especially liver cancer, but also cancer of the esophagus, larynx, stomach, bile ducts, lungs and colon [150]. GGT induces generation of reactive oxygen species through interactions of cysteinyl glycine with free iron [151, 152].

Exposure to Roundup at low doses increased GGT expression in rat testis and Sertoli cells [94]. A comparison between goats fed GM Roundup-Ready solvent-extracted soybean *vs* goats fed a conventional soy equivalent revealed that the male kids born to the goats fed the GM soy had elevated expression of GGT in both liver and kidney ($P < 0.01$) [153]. A study has shown that 70% of GM Roundup-ready soy samples had significant levels of glyphosate, whereas the conventional soy did not [154].

Exposure of Wistar rats to the herbicide Glyphosate-Biocarb over a period of 75 days resulted in liver damage, including elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), suggesting irreversible hepatocyte damage, as well as large deposition of reticulin fibres containing collagen type III [155], suggesting liver fibrosis [156], which is a major risk factor for hepatocarcinogenesis.

Excessive retinoic acid signalling in the liver is expected due to the interference of glyphosate with liver CYP enzymes [11, 157, 158], because the CYP2C gene

family is needed to metabolize retinoic acid in the liver [159]. The action of retinoic acid is likely mediated through sonic hedgehog signalling [160]. Studies on mice have revealed that hedgehog signalling induces fibrosis and hepatocellular carcinoma [161]. Studies on tadpoles have demonstrated that glyphosate produces teratogenic effects characteristic of excessive retinoic acid signalling, and these effects were reversed by a retinoic acid antagonist [162].

12. PANCREATIC CANCER

Pancreatic cancer is one of the cancers whose incidence is going up in step with the increase in glyphosate usage on corn and soy crops ($R = 0.918$; $P \leq 4.6 \times 10^{-7}$.) [1]. As of 2002, pancreatic adenocarcinoma was the fourth leading cause of cancer death in the USA, with an overall 5-year survival rate of less than 5% [163]. We have already noted that excess methylglyoxal exposure can lead to diabetes. Direct evidence of this was obtained when methylglyoxal injection into Sprague Dawley rats caused pancreatic β-cell dysfunction [164]. We earlier discussed the rôle of excess iron deposition in the destruction of pancreatic β cells [134].

Glyphosate's metal chelation effects led to severe manganese deficiency in cows [83]. Rats fed a diet deficient in manganese showed significantly lower concentrations of manganese in liver, kidney, heart and pancreas compared to controls [165]. Pancreatic insulin content was reduced by 63%, and insulin output was correspondingly reduced, suggesting that manganese deficiency may play a direct rôle in insulin-deficient diabetes and islet cell stress.

Acinar cell carcinoma is the second most common type of pancreatic cancer, characterized histologically by zymogen-like granules as well as fibrillary internal structures in the tumour cells [166]. A comparison between mice fed GM soy and wild soy demonstrated alterations in pancreatic acinar cells including smaller zymogen granules and less zymogen content in one month-old mice, along with reduced production of α-amylase [167]. The authors did not consider possible effects of glyphosate contamination, even though another study has shown significant glyphosate residues in GM soy as compared to conventional soy treated with glyphosate [154]. Pancreatic atrophy of the acinar cells along with degranulation and intracellular fibrillation is a fundamental aspect of the childhood wasting disease kwashiorkor [168], which is linked to disrupted gut microbes [169], and may also be in part attributable to glyphosate poisoning.

A two-year study of glyphosate toxicity to rats reported by the EPA in 1991 showed several signs of tumours, which were ultimately dismissed partly because of a lack of a dose–response relationship, and in part because it was argued that historical controls (but not the controls in the study) demonstrated tumours at comparable rates, but under very different and uncontrolled dietary and lifestyle practices [170]. The most frequently observed tumours were pancreatic islet cell adenomas in males, thyroid C-cell adenomas and/or carcinomas in males and females, and hepatocellular adenomas and carcinomas in males. Both low-dose and high-dose, but not mid-dose, males had a statistically significant increased incidence of pancreatic islet cell adenomas.

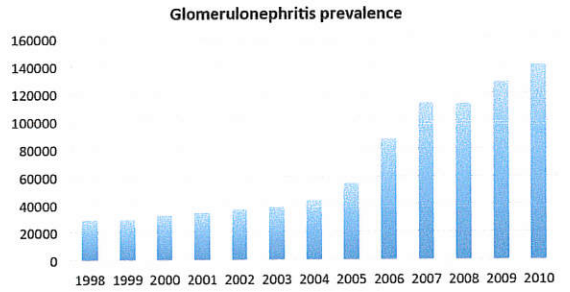

Figure 2. Incidence of nephritis and kidney failure reports in the US CDC's hospital discharge data from 1998 to 2010 normalized to counts per million population each year. This includes all reports of ICD-9 codes from 580 to 589.

13. KIDNEY CANCER

Chronic kidney disease (CKD) and cancer are closely linked in reciprocal fashion: cancer or its treatment can cause CKD and patients with CKD have increased risk of cancer. Dialysis patients have an increased risk ranging from 10% to 80%; kidney transplant recipients have a 3- to 4-fold increased risk of cancer [6]. The number of patients with kidney failure treated by dialysis and transplantation increased dramatically in the USA from 209 000 in 1991 to 472 000 in 2004 [171]. There have been concurrent increases in earlier stages of chronic kidney disease such as albuminuria and impaired glomerular filtration [172]. Since 2004, this trend has worsened. Figure 2 shows the trend over time in the US Centers for Disease Control (CDC)'s hospital discharge data[4] for ICD-9 codes 580-589, including acute and chronic glomerulonephritis, nephritis and nephropathy, acute and chronic renal failure, renal sclerosis, and disorders resulting from impaired renal function. There has been an alarming rise in the frequency of these conditions, especially since 2006.

[4] ftp://ftp.cdc.gov/pub/Health Statistics/NCHS/Datasets/NHDS

Studies on rats show that CYP 2B1 plays a pivotal rôle as an important site for ROS production through cytotoxicity in the glomeruli [173]. The breakdown of the CYP haem protein through attack by H_2O_2 leads to the release of catalytic iron, which, in turn, generates more potent tissue-damaging oxidants such as the hydroxyl radical. Glyphosate's induction of excess H_2O_2 as discussed earlier would cause an increase in the bioavailability of catalytic free iron to work synergistically with H_2O_2 to cause toxicity.

Methylglyoxal and other glycating agents may be a significant factor in the development of kidney disease. Twelve weeks of administration through drinking water of methylglyoxal to Dahl salt-sensitive rats led to an increase in systolic blood pressure and significantly increased urinary albumin excretion, glomerular sclerosis, tubular injury, myocardial collagen content and cardiac perivascular fibrosis [174]. Renal markers of AGE production, oxidative stress and inflammation were all elevated.

Acquired cystic kidney disease (ACKD) can lead to renal tumours, and the tumours often accumulate calcium oxalate crystals [175]. These tumours are often associated with distinctive morphological features, where the tumour cells have ill-defined cell membranes, abundant granular eosinophilic cytoplasm, large nuclei and prominent nucleoli. In another study identifying intratumoral calcium oxalate crystal deposition in two cases of high-grade renal carcinomas, the authors suggested a relationship between tumour growth and oxalate crystal deposition [176]. This suggests a rôle for oxalic acid added to glyphosate-based formulations.

An *in vitro* study on rat testis and Sertoli cells demonstrated that Roundup triggers calcium-mediated cell death associated with reductions in levels of the antioxidant glutathione, along with thiobarbituric acid reactive species (TBARS) and protein carbonyls indicative of protein oxidation and glycation damage [94]. Administration of L-buthionine(S,R)-sulfoximine (BSO), a specific inhibitor of glutathione synthesis, to rats caused reduced glutathione levels in the kidneys and a marked increase in pathologies linked to polycystic kidney disease [177].

14. CATARACTS AND MELANOMA

As we showed previously, Monsanto's own studies revealed increased risk of cataracts following exposure to Roundup. Early-onset cataracts are associated with insufficient antioxidative activity and, therefore, are a potential risk of cancer, as verified in a recent nationwide study based in Taiwan [178].

Methylglyoxal is implicated in cataract development [179, 180]. Methylglyoxal induces endoplasmic reticulum stress in human lens epithelial cells, and activates an unfolded protein response leading to overproduction of ROS. Overexpression of Keap1 protein causes proteasomal degradation of Nrf2, thus suppressing Nrf2-dependent stress protection. As a consequence, the cellular redox balance is altered toward lens oxidation and cataract formation [179].

There is a link between cholestasis and cataracts via poor absorption of nutrients that protect the lens from UV damage. Studies on short-term exposure of catfish to sublethal levels of Roundup revealed toxicity to the gills, liver and kidneys [181]. The observed elevated levels of unconjugated bilirubin and alanine aminotransferase (ALT) are indicative of cholestasis, likely in part a consequence of impaired CYP enzyme function. Cholestasis impairs the absorption of fat-soluble vitamins and previtamins such as the carotenoids [182]. Lutein and zeaxanthin are carotenoids that play an important rôle in the lens and macular region of the retina to protect from oxidative damage due to sunlight exposure [183, 184]. They are highly lipophilic and, therefore, like the fat-soluble vitamins, depend on adequate bile flow for gastrointestinal absorption. Cholestatic patients have greatly reduced serum levels of these nutrients [182].

Tryptophan is a product of the shikimate pathway that glyphosate suppresses. A tryptophan-free diet induces cataracts in young Wistar rats, along with a significant decrease in lens weight and water-soluble lens protein [185]. Kynurenine is a breakdown product of tryptophan, and it has been suggested that kynurenine and its glycoside derivatives in the ocular lens protect the retina from UV light by absorbing UV radiation [186]. Kynurenine is present in excessive concentrations in cataracts [186].

Melanoma is one of the types of cancer that have been linked to glyphosate exposure in agriculture. An age-adjusted analysis revealed an 80% increased risk of melanoma associated with glyphosate use in a study on pesticide applicators in Iowa and North Carolina [187]. It is possible that impaired supply of the aromatic amino acids, tryptophan and tyrosine due to disruption of the shikimate pathway in gut microbes plays a rôle in increased risk to melanoma.

In vitro, exposure to 0.1 mM glyphosate induced hyperproliferation in human skin keratinocytes (HaCaT) cells, suggesting carcinogenic potential [188]. The mechanism involves increased ROS expression and the emptying of intracellular calcium stores, which facilitates basal cell or squamous cell carcinomas. Cells accumulated in S-phase of the cell cycle, while mitochondrial apoptotic signalling pathways were downregulated.

Melanin plays an important protective rôle in the skin against UV exposure, and dark-skinned races have

significantly reduced risk of skin melanoma because of their naturally higher levels of melanin [189]. Melanosomes are tissue-specific organelles in pigment cells that resemble lysosomes, in which melanin is synthesized and stored [190]. L-tyrosine is the precursor to melanin synthesis, and the pathway involves the intermediary, L-dopa. Both L-tyrosine and L-dopa, when supplied to cells with melanogenic potential, increase not only the synthesis of melanin but also the formation of melanosomes within the cells [191].

While blacks have protection against skin cancer due to the high concentration of melanin in their skin, dark skin also appears to be a risk factor for autism. A study based in Los Angeles showed that children born to black foreign-born women had a substantially increased risk for low-functioning autism [192]. A similar observation has been made in Sweden [193] and the UK [194]. One possibility is that increased demand for melanin in the skin depletes the supply of tyrosine for dopamine synthesis. Genetic mutations in dopamine transport proteins have been linked to autism [195, 196]. The defect features a persistent reverse transport of dopamine (substrate efflux from the synapse), which reduces the amount of time extracellular dopamine is available for signalling effects [195]. Other genes of the dopaminergic network are also linked to autism, including syntaxin [197] and enzymes involved in dopamine metabolism [198]. Hence, we hypothesize that reduced bioavailability of tyrosine (due to disruption of the shikimate pathway in gut microbes) for either dopamine synthesis or melanin synthesis leads to different outcomes (autism *vs* melanoma) depending on race-related skin colour.

Tryptophan is an essential amino acid for lymphocyte activation and proliferation, which promotes surveillance and elimination of tumour cells [199, 200]. Tryptophan is also produced by gut microbes via the shikimate pathway that glyphosate disrupts, suggesting that glyphosate exposure to gut microbes could impair tryptophan bioavailability to the human host. The enzyme indoleamine 2,3-dioxygenase (IDO) catalyses the degradation of tryptophan to kynurenines. Tumours of the lung [201], colon [202], liver [203], breast [204] and uvea [205], as well as skin melanoma [206], overexpress IDO, and it is believed that this leads to an ability to evade immune surveillance by T-cells via depletion of tryptophan bioavailability in the surrounding milieu [205]. It is interesting that IDO offers significant protection from UV damage by producing tryptophan-based filters that protect the cornea, lens and retina from UV-induced photo-oxidation [207, 208]. It may well be that tumours exploit IDO for this purpose as well. Clearly, decreased bioavailability of tryptophan due to glyphosate's effects on gut microbes would enhance the tumour's ability to deplete tryptophan and avoid immune surveillance, but might also lead to accelerated DNA damage within the tumour and increased risk of metastasis [209].

15. THYROID CANCER

The incidence of thyroid cancer in the United States has increased dramatically in the past two decades, in step with the increase in glyphosate usage on corn and soy crops ($R = 0.988$, $P \leq 7.6 \times 10^{-9}$) [1]. It is not clear how glyphosate might increase risk of thyroid cancer beyond the general factors already described previously in this paper, but it is possible that impaired selenium incorporation into selenoproteins plays a rôle.

Selenium is an important trace element involved in the protection of cells from oxidative stress, and it is particularly important for the thyroid. Low serum levels of selenium are associated with increased risk of thyroid cancer, and probably play a rôle in carcinogenesis. All three of the deiodinases that convert thyroxine (T4) into triiodothyronine (T3) contain selenocysteine, as do glutathione peroxidase and thioredoxin reductase, which are important antioxidant enzymes essential for protecting thyrocytes from oxidative damage [210].

The microbiome plays an important rôle in incorporating free selenium into selenoproteins, especially selenocysteine. *Lactobacillus reuteri* is a popular species in probiotics, shown to be effective against diarrhoea in children [211], and to inhibit the prooxidant cytokine TNF-α in humans [212]. This species has been found to be especially effective in its ability to produce selenocysteine, and has been proposed to have therapeutic benefit in cases of selenium deficiency [213]. *Lactobacillus* is especially vulnerable to glyphosate due to its crucial and unusual need for manganese as an antioxidant [214, 215], so it is plausible that diminished *Lactobacillus* representation in the gut could lead to an impaired supply of selenocysteine for the thyroid.

16. BREAST CANCER

Breast cancer accounts for one third of cancer diagnoses and 15% of cancer deaths in women in the United States. As mentioned previously, an *in vitro* study has confirmed that glyphosate stimulates proliferation of human breast cancer cells when present in concentrations of parts per trillion [9].[1] This effect is specific to hormone-dependent cell lines, and is mediated by the ability of glyphosate to act as an oestrogenic agent.

One can obtain an estimate of the time trends in breast cancer by looking at the CDC's hospital discharge data. The results show a steady decrease in breast cancer

diagnoses up to 2006, followed by an increase from 2006 to 2010 (the last year for which data are available). The decrease can logically be explained by a growing awareness of the increased risk of breast cancer associated with hormone replacement therapy (HRT). A Women's Health Initiative (WHI) study, published in 2003, showed a 24% increase in invasive breast cancer risk associated with oestrogen/progestin therapy [216]. In direct response to this alarming report, HRT prescriptions in the United States decreased by 38% in 2003. A large study on 1 642 824 women published in 2013, based on the Breast Cancer Surveillance Consortium, revealed that HRT (commonly used to treat symptoms of menopause) increased the risk of breast cancer by 20% in whites, Asians and hispanics, but not in blacks [217].

By forming separate records from the hospital discharge data for black and white women, it can be confirmed that the breast cancer rates among blacks remained flat up to 2006, supporting the observation that black women are not subject to increased risk from HRT. This suggests that one can build a model to correct for the influence of reduced use of HRT among white women in order to arrive at a time trend that might more closely capture any effects of glyphosate. A simple decaying exponential model matches well for the Caucasian data from 1998 to 2006, and this model can be extended into the time interval from 2006 to 2010, and then subtracted from the original plot, to yield a plot of the residual trends for breast cancer. The resulting plot is shown in Fig. 3 alongside rates of glyphosate usage on corn and soy crops. The correlation coefficient is 0.9375 (P-value ≤ 0.0001132).

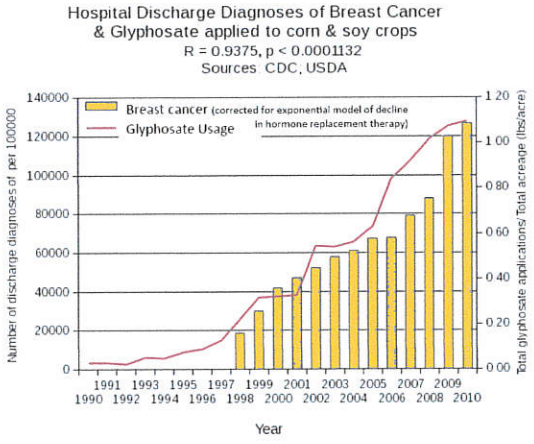

Figure 3. Incidence of breast cancer in US hospital discharge data from 1998 to 2010 normalized to counts per 1,000,000 population each year, after subtraction of an exponential model accounting for the decline in the years up to 2006 in the Caucasian subpopulation [see text]. This includes all reports of ICD-9 codes 174 and 175. The red line shows trends in glyphosate usage on corn and soy crops over the same time period.

A study on rats conducted by Séralini et al. [7] divided the rats into four groups: (1) control, (2) GM maize without Roundup, (3) GM maize with Roundup, and (4) Roundup alone. The major tumours detected in the female rats were mammary fibroadenomas and adenocarcinomas. These authors summaraized their findings as: "The Roundup treatment groups showed the greatest rates of tumour incidence, with 80% of animals affected with up to 3 tumours for one female, in each group." For the group that received Roundup in their drinking water, all but one of the females presented with mammary hypertrophies and hyperplasias. The one exception suffered from a metastatic ovarian carcinoma.

Glyphosate may also indirectly increase risk of breast cancer by impairing metabolism of toxic phenolic compounds such as nonylphenols, diethylstilbestrol (DES), and Bisphenol A (BPA), all widely recognized to possess oestrogenic activity. Nonylphenols, also known as alkylphenols, are a family of organic compounds used extensively as additives in laundry detergents, lubricating oils, paints, pesticides, personal care products and plastics, which are known to be xenoestrogenic [218]. DES is an oestrogenic compound linked to vaginal tumours in women exposed *in utero* to this compound when it was mistakenly believed to be of therapeutic benefit. BPA, commonly used in plastics production, is now widely recognized as an endocrine disruptor. PCBs were widely used as coolants and insulating fluids for transformers and capacitors until their ban in 1979 by the US government due to recognition of their toxicity due to oestrogenic activity. However, they degrade very slowly, and therefore are still environmental pollutants today.

Liver CYP enzymes play an important rôle in metabolizing all of these xenoestrogenic compounds. CYP1A1 is upregulated in response to PCB exposure, and therefore it likely metabolizes these toxic phenols [219]. High serum levels of PCBs in conjunction with at least one (defective) exon 7 variant allele of CYP1A1 increased breast cancer risk [219]. CYP enzymes are also involved with the metabolism of nonylphenols [220]. Similarly, BPA is mainly metabolized by the CYP2C subfamily in the liver [221]. Thus, impaired CYP function due to glyphosate exposure [11, 157, 158] can be expected to interfere with metabolism of PCBs and therefore increase their oestrogenic potential, leading indirectly to increased risk of breast cancer.

High dietary iron enhances the incidence of carcinogen-induced mammary cancer in rats and oestrogen-induced kidney tumours in hamsters [222]. Oestrogen facilitates iron uptake by cells in culture. Elevated body iron storage increases the risk of several cancers, including breast cancer in humans. Although it might be argued that

glyphosate's chelating effects may protect from iron overload, glyphosate could increase the bioavailability of free iron due to its damaging effects on red blood cells [42, 223] working synergistically with its interference in haem synthesis [144], and by acting as an oestrogen mimetic to enhance iron uptake. Haem degradation by reactive oxygen species [224] will lead to the release of free iron, and we have previously discussed how glyphosate would induce oxidative stress. In fact, recent evidence strongly suggests that GGT induces lipid peroxidation of red blood cell membranes leading to haemolysis and the release of free iron from chelating agents [225]. This also results in impaired deformability which impedes their passage through narrow capillaries. GGT was found to be enhanced up to 5.4-fold in the liver in Séralini et al.'s long-term study of rats exposed to GMO's plus Roundup [7].

17. NON-HODGKIN'S LYMPHOMA

Striking increases in the incidence of non-Hodgkin lymphoma (NHL) cancer have occurred over the past three decades, both in Europe [226] and America [227]. Agricultural workers have a higher risk of NHL than the general population, but it is difficult to tease out the effects of glyphosate compared to the myriad other toxic chaemicals they are exposed to, which also confer increased risk [228]. However, some studies have been able to directly link glyphosate to NHL. A threefold increased risk of NHL in association with glyphosate exposure was found in a 2002 study from Sweden [229]. A later Swedish study in 2008 of over 900 cancer cases also found a significant increased risk of NHL (OR 2.02) [230]. A Canadian study demonstrated a correlation between the number of days per year of glyphosate exposure and the risk of NHL [231].

Increased exposure to superoxide is implicated as a causal agent in oncogenesis [232], and manganese SOD (Mn-SOD) is an important antioxidant defence agent in mitochondria [233]. Mice engineered to be defective in Mn-SOD had increased DNA damage and higher cancer incidence [234]. We mentioned earlier that Mn-SOD is protective against pancreatic cancer. Mn-SOD expression was also found to be anomalously low in erythrocytes of patients suffering from NHL [235]. *In vitro* studies have shown that an Mn-SOD mimetic had an anti-proliferation effect on human NHL Raji cells [236]. Glyphosate's chelating effects on manganese can be expected to interfere with Mn-SOD function [82]. Increased Mn-SOD expression potentiates apoptosis of tumour cells exposed to dexamethasone [237]. Cationic manganese porphyrins, probably by acting as Mn-SOD mimetics, have also been found to play a protective rôle in treating NHL [238, 239].

Bone marrow involvement is common in NHL and, particularly for those of T-cell origin, it portends a poor prognosis [240]. An unpublished study by Monsanto in 1983 confirmed that glyphosate administered by intraperitoneal injection to rats reaches the bone marrow within 30 minutes [241]. In an experiment to assess potential toxicity to bone marrow cells [242], a single intraperitoneal dose of glyphosate at concentrations of 25 and 50 mg/kg was administered to Swiss albino mice. Chromosal aberrations and micronuclei, analysed 24, 48, and 72 hours later, were shown to be significantly increased compared to vehicle control ($P < 0.05$). Mitosis rates were also decreased, indicating cytotoxic effects.

Multiple myeloma is the second most common haematological malignancy in the USA after non-Hodgkin lymphoma; it constitutes 1% of all cancers [243]. In a prospective cohort study of 57 311 licensed pesticide applicators in Iowa and North Carolina, a greater than twofold increased risk of multiple myeloma was associated with ever-use of glyphosate [187].

Coeliac disease, along with the more general condition, gluten intolerance, has recently reached epidemic levels in the United States, and it has been hypothesized that this heightened wheat sensitivity is a direct consequence of glyphosate contamination of the wheat, due to the increasingly common practice of wheat desiccation with glyphosate just before harvest [158]. Coeliac disease patients are at increased risk of cancer, particularly non-Hodgkin lymphoma, and they have statistically a shortened lifespan mainly due to this increased cancer risk.

For coeliac disease patients, serum prolactin (PRL) levels are high in association with an unrestricted gluten-containing diet, and PRL has been proposed as a useful marker for coeliac disease [244]. PRL is an important regulatory hormone released by the pituitary gland, which is best known for inducing lactation. Bisphenol A, a well-established oestrogenic agent, has been shown to lead to hyperprolactinaemia and growth of prolactin-producing pituitary cells [245]. Prolonged exposure to Bisphenol A during childhood may contribute to the growth of a prolactinoma, the most common form of cancer of the pituitary. Oestrogen treatment of ovariectomized rats induced a marked elevation of serum PRL levels [246], and this was found to be due to oestrogen's ability to reduce the capacity of PRL cells to incorporate dopamine into their secretory granules. Since glyphosate has been confirmed to be oestrogenic, it is plausible that glyphosate contamination in wheat is the true source of the observed elevation of PRL in association with gluten ingestion among coeliac patients.

18. CONCLUSION

In this paper, we have reviewed the research literature on glyphosate and on the biological processes associated with cancer, and we have provided strong evidence that glyphosate is likely contributing to the increased prevalence of multiple types of cancer in humans. Monsanto's own early studies revealed some trends in animal models that should not have been ignored. Forty years of glyphosate exposure have provided a living laboratory where humans are the guinea pigs and the outcomes are alarmingly apparent.

We have shown that glyphosate transforms exposed cells into a tumour-provoking state by suppressing crucial enzymes in the electron transport chain, such as succinate dehydrogenase and fumarate hydratase. Glyphosate chelates manganese, reducing its bioavailability, and manganese is an important catalyst for Mn-SOD, which protects mitochondria from oxidative damage, which can cause mutations in DNA. Glyphosate also causes impaired metabolism of fructose, due to the accumulation of PEP following blockage of the shikimate pathway. This leads to the synthesis of multiple short-chain sugars that are known to be highly potent glycating agents, such as methylglyoxal and glyoxalate. Glyphosate is readily nitrosylated, and nitrosyl glyphosate is known to be extremely toxic and carcinogenic. Microbial pathways convert glyphosate into sarcosine, a known marker for prostate cancer, likely due to its nitrosylated form.

An often overlooked aspect of glyphosate's toxicity is its interference with enzymes that have glycine as substrate, due to mimicry. Phenolic compounds are detoxified by gut microbes through glycine conjugation to produce products such as hippurate. Bifidobacteria are important for the rôle they play in protecting from these xenobiotics through such conjugation. Reduced hippurate is linked to Crohn's diseases and inflammatory bowel disease, which show epidemiological trends that match the increased use of glyphosate on core crops, and which are linked to increased risk of a broad range of cancers, most especially non-Hodgkin lymphoma. Lymphoma has also been linked to glyphosate through studies of environmental exposure in agricultural settings.

Multiple studies, both *in vitro* and *in vivo*, have shown that glyphosate damages DNA, a direct step towards tumorigenicity. These studies have been conducted on sea urchins, fish, mice and various human cell types *in vitro*. Children in Malaysia living near rice paddies have evidence of DNA damage.

Epidemiological studies strongly support links between glyphosate and multiple cancers, with extremely well matched upward trends in multiple forms of cancer in step with the increased use of glyphosate on corn and soy crops. While these strong correlations cannot prove causality, the biological evidence is strong to support mechanisms that are likely in play, which can explain the observed correlations through plausible scientific arguments.

Glyphosate's links to specific cancer types can often be explained through specific pathologies. For example, succinate dehydrogenase deficiency is linked to adrenal cancer [17]. Selenoprotein deficiency is likely contributory towards thyroid cancer. Glyphosate's action as an oestrogen mimetic explains increased breast cancer risk. Prostate cancer is linked to sarcosine, a by-product of glyphosate breakdown by gut microbes. Impaired fructose metabolism links to fatty liver disease, which is a risk factor for hepatic tumorigenesis. Impaired melanin synthesis by melanocytes due to deficiencies in the precursor, tyrosine, a product of the shikimate pathway, can explain increased incidence of skin melanoma. This is compounded by tryptophan deficiency, as tryptophan is also protective against UV exposure.

Manganese deficiency stresses the pancreas and impairs insulin synthesis, and this could explain the recent epidemic in pancreatic cancer. Increased oxalate, due in part to the proprietary formulations, stresses the kidney and contributes to risk of renal tumours. Glyphosate's accumulation in bone marrow can be expected to disrupt the maturation process of lymphocytes from stem cell precursors. Glycine forms conjugates with organic benzene-derived carcinogenic agents, and glyphosate likely interferes with this process. Glyphosate's interference with CYP enzyme function impairs detoxification of multiple other carcinogenic agents, increasing their carcinogenic potential. Overall, the evidence of the carcinogenicity of glyphosate is compelling and multifactorial.

APPENDIX: NEOPLASTIC INCIDENCE DATA FROM MONSANTO

Two-Year Animal Studies

In this section we present selected tables tabulating tumours and malignancies, separately for male and female rats, in the long-term study conducted by Lankas & Hogan and reported on in an unpublished document in 1981 [17]. The rats were exposed to three different doses of glyphosate added to their feed (3, 10, and 30 mg kg^{-1} day^{-1}) and compared with unexposed controls.

Similarly, we present tables tabulating all of the tumours and malignancies that were found, separately for male and female mice, in the long-term study conducted by Knezevich & Hogan and reported on in an unpublished document in 1983 [18]. The mice were exposed to three different doses of glyphosate added to their feed (1000, 5000 and 30 000 ppm) and compared with unexposed controls.

Table A1. Incidence of neoplastic findings in male rats with glyphosate administered by diet. Part I. Data extracted from Lankas & Hogan (1981) [17].

Glyphosate /mg kg^{-1} day^{-1}	0	3	10	30
		PITUITARY		
Adenoma	16/48 (33%)	19/49 (38%)	20/48 (40%)	18/47 (36%)
Carcinoma	3/48 (6%)	2/49 (4%)	3/48 (6%)	1/47 (2%)
		BRAIN		
Glioma	1/49 (2%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
		HEART		
Reticulum cell sarcoma	0/49 (0%)	0/49 (0%)	1/50 (2%)	0/50 (0%)
		LUNG		
Sarcoma 0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (2%)	1/50 (2%)
Reticulum cell sarcoma	1/50 (2%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
MS[a] Malignant mixed tumour	0/50 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
		MANDIBULAR SALIVARY GLAND		
Reticulum cell sarcoma	0/49 (0%)	0/49 (0%)	1/49 (2%)	0/49 (0%)
		MEDIASTINAL LYMPH NODE		
MS[a] Fibrosarcoma	0/39 (0%)	0/39 (0%)	1/32 (3%)	0/35 (0%)
Reticulum cell sarcoma	1/39 (3%)	0/39 (0%)	1/32 (3%)	0/35 (0%)
		SPLEEN		
Reticulum cell sarcoma	0/50 (0%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
		STOMACH		
Squamous cell carcinoma, Cardia	0/50 (0%)	0/49 (0%)	0/48 (0%)	1/49 (2%)
		JEJUNUM		
Reticulum cell sarcoma	0/49 (0%)	0/46 (0%)	1/48 (2%)	0/49 (0%)
		KIDNEY		
Tubular adenoma	1/50 (2%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Reticulum cell sarcoma	1/50 (2%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Lipoma	1/50 (2%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
		TESTES		
Interstitial cell tumour	0/50 (0%)	3/50 (6%)	1/50 (2%)	6/50 (12%)

[a]MS = metastatic.

Table A2. Incidence of neoplastic findings in male rats with glyphosate administered by diet. Part II. Data extracted from Lankas & Hogan (1981) [17].

Glyphosate /mg kg^{-1} day^{-1}	0	3	10	30
	PROSTATE			
Reticulum cell sarcoma	0/50 (0%)	0/47 (0%)	1/49 (2%)	0/49 (0%)
	URINARY BLADDER			
Papilloma	0/46 (0%)	1/45 (2%)	0/43 (0%)	0/46 (0%)
	THYROID			
C-cell carcinoma	0/47 (0%)	0/49 (0%)	1/49 (2%)	0/49 (0%)
Follicular adenoma	1/47 (2%)	2/49 (4%)	4/49 (8%)	4/49 (8%)
	PARATHYROID			
Adenoma	0/27 (0%)	2/30 (4%)	0/28 (0%)	0/27 (0%)
	ADRENAL			
Reticulum cell sarcoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Pheochromo-cytoma	8/50 (16%)	8/50 (16%)	5/50 (10%)	11/50 (22%)
Cortical adenoma	2/50 (4%)	4/50 (8%)	1/50 (2%)	1/50 (2%)
	SKIN			
Basosquamous cell tumour	0/49 (0%)	0/48 (0%)	0/49 (0%)	1/49 (2%)
Sebaceous gland adenoma	0/49 (0%)	0/48 (0%)	0/49 (0%)	1/49 (2%)
	PERIOCULAR TISSUE			
Squamous cell carcinoma	0/0 (0%)	0/0 (0%)	1/1 (100%)	0/0 (0%)
	SUBCUTANEOUS TISSUE			
Fibrosarcoma	2/10 (20%)	1/12 (8%)	2/10 (20%)	3/7 (43%)
Fibroma	0/10 (0%)	3/12 (24%)	1/10 (10%)	2/7 (29%)
Neuro brosarcoma	0/10 (0%)	0/12 (0%)	0/10 (0%)	1/7 (14%)
Lipoma	1/10 (10%)	2/12 (17%)	0/10 (0%)	0/7 (0%)
Osteogenic sarcoma	0/10 (0%)	0/12 (0%)	1/10 (10%)	0/7 (0%)
Malignant mixed tumour	0/10 (0%)	1/12 (8%)	0/10 (0%)	0/7 (0%)
	MEDIASTINAL TISSUE			
Reticulum cell sarcoma	0/7 (0%)	0/1 (0%)	0/4 (0%)	1/2 (50%)
	ABDOMEN			
Lipoma	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)
	ABDOMINAL CAVITY			
Reticulum cell sarcoma	0/0 (0%)	0/0 (0%)	1/1 (100%)	0/0 (0%)
	LUMBAR LYMPH NODE			
MS[a] Islet cell carcinoma	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)
	SACRAL LYMPH NODE			
Reticulum cell sarcoma	0/1 (0%)	1/3 (33%)	0/3 (0%)	0/3 (0%)

[a]MS = metastatic.

Table A3. Incidence of neoplastic findings in female rats with glyphosate administered by diet. Part I. Data extracted from Lankas & Hogan (1981) [17].

Glyphosate /mg kg^{-1} day^{-1}	0	3	10	30
	PITUITARY			
Carcinoma	8/48 (17%)	7/48 (15%)	5/50 (10%)	12/49 (24%)
	BRAIN			
Invasive pituitary carcinoma	0/50 (0%)	0/49 (0%)	1/50 (2%)	1/50 (2%)
Malignant lymphoma	0/50 (0%)	0/49 (0%)	0/50 (0%)	1/50 (2%)
Glioma	0/50 (0%)	0/49 (0%)	0/50 (0%)	1/50 (2%)
	CERVICAL SPINAL CORD			
Malignant lymphoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
	HEART			
Malignant lymphoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
	LUNG			
Reticulum cell sarcoma	2/49 (4%)	2/50 (4%)	1/49 (2%)	3/50 (6%)
Malignant lymphoma	0/49 (0%)	1/50 (2%)	0/49 (0%)	1/50 (2%)
Adenocarcinoma	0/49 (0%)	0/50 (0%)	0/49 (0%)	1/50 (2%)
Carcinoma	0/49 (0%)	0/50 (0%)	1/49 (2%)	0/50 (0%)
	LIVER			
Reticulum cell sarcoma	2/50 (4%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Malignant lymphoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Hepatocellular carcinoma	1/50 (2%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
	MESENTERIC LYMPH NODE			
Malignant lymphoma	0/42 (0%)	0/39 (0%)	0/48 (0%)	1/47 (2%)
Reticulum cell sarcoma	0/42 (0%)	0/39 (0%)	0/48 (0%)	2/47 (4%)
	PANCREAS			
Islet cell carcinoma	0/50 (0%)	1/50 (2%)	1/50 (2%)	1/49 (2%)
	MANDIBULAR SALIVARY GLAND			
Metastatic fibrosarcoma	0/48 (0%)	0/50 (0%)	1/49 (2%)	0/49 (0%)
	THYMUS			
Malignant lymphoma	0/25 (0%)	0/32 (0%)	1/37 (3%)	1/34 (3%)
Thymoma	0/25 (0%)	0/32 (0%)	1/37 (3%)	0/34 (0%)
	MEDIASTINAL LYMPH NODE			
Reticulum cell sarcoma	0/33 (0%)	1/29 (3%)	0/37 (0%)	0/30 (0%)
Malignant lymphoma	0/33 (0%)	0/29 (0%)	1/37 (3%)	2/30 (7%)
	SPLEEN			
Malignant lymphoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Reticulum cell sarcoma	2/50 (4%)	2/50 (4%)	1/50 (2%)	5/50 (10%)
	STOMACH			
Malignant lymphoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
	JEJUNUM			
Leiomyosarcoma	0/50 (0%)	1/48 (2%)	0/49 (0%)	0/49 (0%)
	ILEUM			
Reticulum cell sarcoma	0/47 (0%)	0/49 (0%)	0/49 (0%)	1/48 (2%)
	COLON			
Reticulum cell sarcoma	0/50 (0%)	0/50 (0%)	0/49 (0%)	1/48 (2%)
	URINARY BLADDER			
Transitional cell tumour	0/50 (0%)	0/48 (0%)	0/48 (0%)	1/44 (2%)

Table A4. Incidence of neoplastic findings in female rats with glyphosate administered by diet. Part II. Data extracted from Lankas & Hogan (1981) [17].

Glyphosate /mg kg^{-1} day^{-1}	0	3	10	30
	OVARY			
Granulosa cell tumour	8/49 (16%)	8/50 (16%)	6/48 (13%)	6/45 (13%)
Theca-granulosa cell tumour	0/49 (0%)	0/50 (0%)	0/48 (0%)	1/45 (2%)
	UTERUS			
Squamous cell carcinoma	0/50 (0%)	0/50 (0%)	0/49 (0%)	1/49 (2%)
Endometrial sarcoma	0/50 (0%)	0/50 (0%)	0/49 (0%)	1/49 (2%)
Adenoma	0/50 (0%)	0/50 (0%)	2/49 (4%)	1/49 (2%)
	THYROID			
C-cell adenoma	5/47 (10%)	3/49 (6%)	6/50 (12%)	3/47 (6%)
C-cell carcinoma	1/47 (2%)	0/49 (0%)	2/50 (4%)	6/47 (12%)
Metastatic fibrosarcoma	0/47 (0%)	0/49 (0%)	1/50 (2%)	0/47 (0%)
	PARATHYROID			
Adenoma	0/23 (0%)	0/25 (0%)	0/25 (0%)	1/23 (4%)
	ADRENAL			
Reticulum cell sarcoma	1/50 (2%)	1/50 (2%)	1/50 (2%)	3/49 (6%)
Pheochromo-cytoma	1/50 (2%)	2/50 (4%)	2/50 (4%)	2/49 (4%)
Cortical adenoma	5/50 (10%)	10/50 (20%)	6/50 (12%)	4/49 (8%)
Malignant lymphoma	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/49 (2%)
	MAMMARY GLAND (L&R)			
Adenoma (L)	4(47) (8%)	7(46) (15%)	10(48) (20%)	5(44) (11%)
Adenoma (R)	4(47) (8%)	7(46) (15%)	8(48) (16%)	5(44) (11%)
Fibroadenoama (L)	33/47) (66%)	28(46) (61%)	27(48) (56%)	22(44) (50%)
Fibroadenoama (R)	24(47) (48%)	16(46) (35%)	20(48) (41%)	16/44 (36%)
	EYE			
Periocular fibrosarcoma	0/49 (0%)	0/48 (0%)	1/50 (2%)	0/47 (0%)
	HARDERIAN GLAND			
Malignant lymphoma	0/47 (0%)	0/45 (0%)	0/47 (0%)	1/44 (2%)
Invasive fibrosarcoma	0/47 (0%)	0/45 (0%)	1/47 (2%)	0/44 (0%
	BONE MARROW			
Malignant lymphoma	0/46 (0%)	0/44 (0%)	1/46 (2%)	1/45 (2%)
Reticulum cell sarcoma	1/46 (2%)	0/44 (0%)	1/46 (2%)	3/45 (6%)
	SUBCUTANEOUS TISSUE			
Lipoma	0/4 (0%)	0/6 (0%)	0/1 (0%)	2/2 (100%)
Reticulum cell sarcoma	0/4 (0%)	2/6 (33%)	0/1 (0%)	0/2 (0%)
	MEDIASTINAL TISSUE			
Reticulum cell sarcoma	0/2 (0%)	1/1 (100%)	0/2 (0%)	0/2 (0%)
	MESENTERY			
Reticulum cell sarcoma	0/5 (0%)	0/5 (0%)	0/2 (0%)	2/7 (29%)
	MANDIBULAR LYMPH NODE			
Malignant lymphoma	0/2 (0%)	0/3 (0%)	0/6 (0%)	1/6 (17%)
	URETER			
Transitional cell carcinoma	0/0 (0%)	0/0 (0%)	1/1 (100%)	1/1 (100%)

Table A5. Incidence of neoplastic findings in male mice with glyphosate administered by diet. Part I. From Knezevich & Hogan, 1983 [18]. BN = Benign, MG = Malignant, MS = Metastatic.

Glyphosate (ppm)	0	Low (1000)	Mid (5000)	High (30000)
		BRAIN		
MS Lymphoblastic lymphosarcoma with leukaemic manifestations	0/49 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
		HEART		
MS Lymphoblastic lymphosarcoma with leukaemic manifestations	0/47 (0%)	1/49 (2%)	2/49 (4%)	1/50 (2%)
		LUNGS		
BN Bronchiolar-alveolar adenoma	5/48 (10%)	9/50 (18%)	9/50 (18%)	9/50 (18%)
MG Bronchiolar-alveolar adeno-carcinoma	4/48 (8%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
MS Lymphoblastic lymphosarcoma with leukaemic manifestations	1/48 (2%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
MS Lymphoblastic lymphosarcoma	0/48 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
		LIVER		
MG Hepatocellular adenocarcinoma	5/49 (10%)	6/50 (12%)	6/50 (12%)	4/50 (8%)
BN Hepatocellular adenoma	0/49 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
MG Hepatocellular carcinoma	0/49 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
MS Histiocytic sarcoma	0/49 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
MS Liposarcoma	0/49 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
MS Lymphoblastic lymphosarcoma with leukaemic manifestations	1/49 (2%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
		MESENTERIC LYMPH NODES		
MG Histiocytic Sarcoma with leukaemic manifestations	0/40 (0%)	1/50 (2%)	0/46 (0%)	0/49 (0%)
MG Lymphoblastic lymphosarcoma with leukaemic manifestations	1/40 (2%)	2/50 (4%)	1/46 (2%)	0/49 (0%)
MS Lymphoblastic lymphosarcoma with leukaemic manifestations	0/40 (0%)	0/50 (0%)	1/46 (2%)	2/49 (4%)
MG Lymphoblastic lymphosarcoma	0/40 (0%)	1/50 (2%)	0/46 (0%)	0/49 (0%)
		MEDIASTINAL LYMPH NODES		
MS Histiocytic sarcoma	0/45 (0%)	1/49 (2%)	0/41 (0%)	0/49 (0%)
MS Lymphoblastic lymphosarcoma with leukaemic manifestations	1/45 (2%)	2/49 (4%)	1/41 (2%)	2/49 (4%)
MG Lymphoblastic lymphosarcoma with leukaemic manifestations	0/45 (0%)	0/49 (0%)	2/41 (5%)	0/49 (0%)